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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/691,237	10/19/2000	David S. Wells	085747/0170	5026

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 08/12/2002 12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/691,237	Applicant(s) WELLS ET AL.	
	Examiner Lakshmi S Channavajjala	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt of Information Disclosure Statement, dated 12-20-01, request for extension of time and amendment B, both dated 5-20-02, is acknowledged.

The following rejection of record (paper # 11) has been maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-11, 14-20, 22-27 and 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rork et al (5,582,838) OR Rork in view of Balandrin et al (5,506,268) OR Balandrin in view of Rork et al.

Rork teaches sustained release formulations, such as tablets, comprising a compressed core and a coating around the core. The core comprises a mixture of physiologically active agent and a polymer such as sodium acrylate polymers or carboxymethylenes prepared from acrylic acid cross-linked with allylic ethers, that on hydration forms polymer gel beads (claims and col. 4, lines 53-68). The formulations delivers drug at a constant rate over four to twenty-four hour period (see figures). Rork suggests a number of physiologically active substances in their formulation, which include hypnotics and sedatives such as diethylisovaleramide or bromo-isovaleryl-urea. The admixture of drug and polymer reads on the matrix of the instant claims.

Rork also teaches that the coating around the core is impermeable and insoluble and forms films (col. 11) and the coating includes plasticizers (claims). Further, Rork teaches polymer coating be made of polymers such as ethyl cellulose, cellulose acetate etc (claim 11). Rork does not explicitly teach that the matrix dissolves slowly or resists hydration. However, absent evidence on contrary, the polymer of Rork also dissolves slowly because the polymer of Rork also forms a gel as in the instant claims. Rork teaches that any pharmaceutically active agent can be used in their sustained formulation and in particular mentions sedatives and hypnotics such as diethylisovaleramide. Therefore, it would have been obvious for a skilled artisan at the time of the instant invention to prepare sustained release formulations of diethylisovaleramide, by preparing a core comprising diethylisovaleramide and a gelling polymer, surrounded by a film coating, with an expectation to provide a constant and sustained release of diethylisovaleramide, such that the sedation or hypnotic effect of diethyisovaleramide is achieved for a long period of time. Rork teaches diethylisovaleramide and not isovaleramide. However, instant claim 1 recites a pharmaceutically acceptable amide of isovaleric acid, which includes the diethylisovaleramide of Rork.

Balandrin teaches isovaleramide as an anxiolytic agent and a sedative and suggests using it for the treatment of central nervous disorders such as tension, restlessness, inability to concentrate, over-aggressiveness etc (col. 6). Balandrin teaches oral administration of isovaleramide in the form of tablets, capsules or drops etc (col. 7). Therefore, it would have been obvious for a skilled artisan at the time of the instant invention to use isovaleramide of Balandrin or diethylisovaleramide of Rork in the sustained release composition of Rork with an expectation to provide a prolonged therapeutic effect for the treatment of CNS disorders taught by Balandrin.

Alternatively, Balandrin teaches isovaleramide for a number of other CNS disorders, but does not teach sustained release compositions. However, it would have been obvious for a skilled artisan at the time of the instant invention to use the sustained release polymer and film coating s of Rork in preparing a formulation of isovaleramide of Balandrin, with an expectation to provide a sustained release of isovaleramide for a prolonged treatment of CNS disorders such as anxiety, restlessness etc.

Claims 6, 12, 21 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rork et al and Balandrin et al as applied to claim1-5, 7-11, 14-20, 22-27 and 29-34 above, and further in view of Pankhania et al (5,415,871).

Neither Balandrin nor Rork teach xanthan gum as a gelling agent.

Pankhania teaches xanthan gum as a gelling agent in sustained formulations for various pharmaceutically active agents such as sedatives, cardiovascular agents etc (col. 4, lines 25-45). Pankhania suggests that xanthan gum hydrates and swells upon exposure to water, to form a gel, and allows a slow and sustained release of the active agent into the body, for as long as 24 hours or longer (col. 2 and col. 4). Pankhania also teaches that xanthan gum avoids the problems of hydrating too rapidly or too slowly and thus does not exhibit the problems of breaking up of the tablet (col. 2). Therefore, it would have been obvious for a skilled artisan at the time of the instant invention to use xanthan gum a gel forming polymer in the sustained release composition of Rork, containing diethylisovaleramide (Rork) or isovaleramide (Balandrin), because Pankhania suggests that xanthan gum as a gelling agent exhibits optimum hydration properties

and the sustained release of the drug from xanthan gum containing formulation has a release profile which is independent of temperature, pH and also allows a steady diffusion of the drug.

Response to Arguments

Applicant's arguments filed 5-20-02 have been fully considered but they are not persuasive.

Applicants argue that Balandrin et al is silent regarding the duration of the anxiolytic or sedative effects of isovaleramide, without which applicants submit that one of an ordinary skill in the art, would not consider a sustained relelase isovaleramide tablet to be either beneficial or desirable. Further, applicants argue that it is indeed applicant's own disclosure that the orally administered isovaleramide has a short half-life in humans and hence examiner's motivation to make a sustained release formulation is based on the hindsight. However, In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, Balandrin teaches isovaleramide containing pharmaceutical compositions in the form of tablets, capsules etc., but does not teach sustained relelase dosage forms. Rork et al suggests controlled release compositions, which applicants also agree. Applicants did not argue the fact that the polymeric matrix materials, coating polymers, core taught by Rork read on the instant claimed materials. Applicants argue that Rork teaches hundreds of compounds for

incorporating into controlled release systems without discrimination and does not specify why such as sustained tablet is desirable for those drugs. However, Rork clearly explains that there exists a need for systems that deliver both soluble and insoluble pharmaceutically active ingredients at a constant rate, over a four to twenty-four hour period. Further, Rork also suggests hypnotics and sedatives, the same class of drugs that isovaleramide (taught by Balandrin) belongs to, as specific examples of drugs that can be incorporated in the sustained/controlled release composition. With respect to applicants' argument that there is nothing in Rork's teachings to particularly direct one of skill in the art to applicants' compounds, in col. 6, lines 2-4, Rork clearly mentions diethylisovaleramide, a compound that belongs to the same class as isovaleramide. Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to incorporate isovaleramide of Balandrin in the controlled (sustained) release composition of Rork, with an expectation to provide a sustained release of isovaleramide and thus a prolonged hypnotic and sedative effect.

With respect to the rejections of claims 6, 12, 13, 21 and 28, applicants argue that the combination of Balandrin and Rork does not render the instant claims obvious and that the teaching of xanthan gum, as a gelling agent does not supply the necessary motivation to the claimed invention. However, the motivation for the combination of the teachings of Balandrin and Rork has been explained. Further, the motivation to add xanthan gum of Pankhania to the composition containing isovaleramide has been explained. Therefore, the rejection is deemed to be proper.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S Channavajjala whose telephone number is 703-308-2438. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-7924 for regular communications and 703-308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Lakshmi S Channavajjala
Examiner
Art Unit 1615
July 29, 2002

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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